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PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing *(day/month/year)* see form PCT/ISA/210 (second sheet)	
Applicant's or agent's file reference see form PCT/ISA/220	**FOR FURTHER ACTION** See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP2005/050417	01.02.2005	04.02.2004

International Patent Classification (IPC) or both national classification and IPC
C07D401/04, C07D401/14, A61K31/498, A61P11/00

Applicant
ALTANA PHARMA AG

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☒ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☒ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☒ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notifed the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:	Authorized Officer
European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Weisbrod, T Telephone No. +49 89 2399-8931

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/EP2005/050417

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material:

   ☐ a sequence listing

   ☐ table(s) related to the sequence listing

   b. format of material:

   ☐ in written format

   ☐ in computer readable form

   c. time of filing/furnishing:

   ☐ contained in the international application as filed.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

Box No. II Priority

1. ☐ The validity of the priority claim has not been considered because the International Searching Authority does not have in its possession a copy of the earlier application whose priority has been claimed or, where required, a translation of that earlier application. This opinion has nevertheless been established on the assumption that the relevant date (Rules 43*bis*.1 and 64.1) is the claimed priority date.

2. ☐ This opinion has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rules 43*bis*.1 and 64.1). Thus for the purposes of this opinion, the international filing date indicated above is considered to be the relevant date.

3. Additional observations, if necessary:

   see separate sheet

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 15-16

because:

☒ the said international application, or the said claims Nos. 15-16 relate to the following subject matter which does not require an international preliminary examination *(specify)*:

see separate sheet

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the whole application or for said claims Nos.

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form	☐	has not been furnished
	☐	does not comply with the standard
the computer readable form	☐	has not been furnished
	☐	does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

Box No. IV Lack of unity of invention

1. ☐ In response to the invitation (Form PCT/ISA/206) to pay additional fees, the applicant has:

   ☐ paid additional fees.

   ☐ paid additional fees under protest.

   ☐ not paid additional fees.

2. ☒ This Authority found that the requirement of unity of invention is not complied with and chose not to invite the applicant to pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rule 13.1, 13.2 and 13.3 is

   ☐ complied with

   ☒ not complied with for the following reasons:

   see separate sheet

4. Consequently, this report has been established in respect of the following parts of the international application:

   ☒ all parts.

   ☐ the parts relating to claims Nos.

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	2-10
	No:	Claims	1,11-16
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-16
Industrial applicability (IA)	Yes:	Claims	1-14
	No:	Claims	

2. Citations and explanations

   see separate sheet

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY (SEPARATE SHEET)

International application No.
PCT/EP2005/050417

Re Item I
Basis of the opinion

The application relates to
(i) phtalazinones (1) (claims 1-11),
(ii) the medical use of compounds (1) (claim 12),
(iii) a pharmaceutical composition comprising a compound (1) (claim 13),
(iv) the second medical use of compounds (1) (claim 14), and
(v) the corresponding therapeutic methods (claims 15-16).

Re Item II
Priority

The claimed date of priority does not appear valid for the present claims 2-4, 8, and 10 and for subject matter referring to these claims.

Re Item III
Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Claims 15 and 16 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

Re Item IV
Lack of unity of invention

See item V.3 below.

Re Item V
Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1 Reference is made to the following document.

D1: WO 02/064584 A, 22.08.2002; cited in the application.

2 Novelty

D1 discloses already PDE4 inhibitors which comprise the present compounds (1) wherein R^9 is OH (cf. D1, claim 1: $R^9 = C(O)R^{13}$ with R^{13} = hydroxy-carbonyl-1-4C-alkyl; and page 13, example no. 4 as specific embodiment within the overlapping range). The present claims 1 and 11-16 lack thus novelty in view of **D1** for the whole overlapping range.

3 Unity of Invention

The application as filed is considered to lack unity of invention since its subject-matter relates not to one but rather to three separate inventions not linked together by a common underlying inventive concept as required by Rules 13.1 and 13.2 PCT. The claims and inventions to which the separate inventions relate are grouped as follows (in the order chosen by the applicant).

(1) Claims 1, 6, and 11-16 (all part) directed to compounds (1) wherein R^9 = OH and n = 0, as well as subject matter referring to such compounds (1);

(2) Claims 1-3, 6, and 11-16 (all part) directed to compounds (1) wherein R^9 = 1-4C-alkoxy, as well as subject matter referring to such compounds (1);

(3) Claims 1-3, 6, 11-16 (all part) and 4, 5, 7-10 (all complete) directed to compounds (1) wherein $R^9 = NHR^{10}$, $NR^{13}R^{14}$ or $NH\text{-}NR^{11}R^{12}$, as well as subject matter referring to such compounds (1).

The identified three inventions involve the technical feature of a "2-(1-R^9-C(O)-$(CH_2)_n$-C(O)-piperidin-4-yl-substituted phthalazinon" as the sole common link. However, this feature cannot be accepted to constitute a special technical feature because it does not define a contribution over the prior art. **D1** discloses already 2-(1-R^9-C(O)-$(CH_2)_n$-C(O)-piperidin-4-yl-phthalazinones wherein R^9 is OH and n is 1-4 as PDE4 inhibitors

(cf. claim 1 and example 4). In view of said prior art the problem underlying the present application may be seen in the provision of further PDE4 inhibitors. The contributions claimed in the present application which are possibly made over the prior art are:

(a) the provision of further PDE4 inhibitors by modifying n in the (R^{13})hydroxy-carbonyl-1-4C-alkyl group of the compounds of **D1**;

(b) the provision of further PDE4 inhibitors by esterifying the hydroxy function of the (R^{13})hydroxycarbonyl-1-4C-alkyl group of the compounds of **D1**; and

(c) the provision of further PDE4 inhibitors by replacing the hydroxy function of the (R^{13})hydroxycarbonyl-1-4C-alkyl group of the compounds of **D1** with a nitrogen derived substituent.

These contributions, however, have nothing more in common than each single of these contributions has in common with the prior art. Consequently, starting from **D1**, these contributions diverge in three different directions and are not so linked as to form one single inventive concept, which would support the unity of the invention.

4 Inventive Step

Insofar as the application relates to novel subject matter the following observations apply to the requirements of inventive step.

4.1 The application describes the preparation of certain compounds (1) and shows that such compounds exhibit PDE4 inhibitory activity (cf. page 39, table 1).

4.2 Starting from **D1** as most relevant state of the art the problem underlying the application my be seen in the provision of further PDE4 inhibitors. Due to the very close structural relationship between the claimed compounds (1) and the compounds of **D1** the claimed compounds would appear to represent merely obvious alternatives of the compounds of the prior art **D1**. In the absence of any common novel feature of the claimed compounds which is shown to contribute to any unexpected property

versus the respective closest related compound of the prior art (e.g. the present (4aS,8aR) compound (1) wherein $R^1 = R^2 = H$, R^3 = 3,4-diethoxyphenyl, $R^9 = OH$, and n = 0; the present (4aS,8aR) compound (1) wherein $R^1 = R^2 = H$, R^3 = 3,4-diethoxyphenyl, $R^9 = OCH_3$, and n = 3; and the present (4aS,8aR) compound (1) wherein $R^1 = R^2 = H$, R^3 = 3,4-diethoxyphenyl, $R^9 = NHCH_3$, and n = 3; each in comparison with example 4 of **D1**), the present claimed subject matter does not appear to involve an inventive step. Hence, the claims 1-16 do at present not meet the requirements of Article 33(3) PCT.

5 Industrial Applicability

For the assessment of the present claims 15 and 16 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

Re Item VIII

Certain observations on the international application

Present claim 15 is to be objected under Article 6 PCT, because the therapeutic method is functionally defined by a mechanism of action which does not allow any practical application in the form of a defined, real treatment of a pathological condition. The objection could be overcome by either introducing in the claims a list of pathological conditions cited in the application, or by showing that means are available which would allow the skilled person to recognise which additional conditions would fall within the functional definition.